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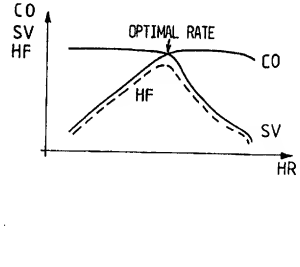
(57) Abstract

In the determination of an optimal rate for the delivery of stimulation pulses to a heart, the stroke volume (SV) of a heart ventricle is measured as a function of heart rate (HR), e.g. by determination of impedance in individual heart cycles whose duration is varied from the duration corresponding to the prevailing rate or the basic rate regarded as optimal for stimulation. The optimal rate should lie at the knee of this function. A corresponding knee is also found in the curve for cardiac output (CO). This rate is determined by calculation of an auxiliary function, e.g. HF = HR . CO, which displays a peak at the heart rate at which the knee is located, and the heart rate is determined which yields this maximum. The heart rate determined in this manner is subsequently employed as a basic rate.



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Heart stimulation device

FIELD OF THE INVENTION

The present invention relates to devices for determining the optimal rate for emission of a stimulation pulse to a heart

BACKGROUND OF THE INVENTION AND THE PRIOR ART

The ability to control the heart rate by means of electrical stimulation is important to the well-being and survival of many people afflicted by various defects in the function of their hearts. Battery-powered stimulation devices are available for different kinds of disorders.

The heart comprises a left atrium, right atrium, left ventricle and right ventricle and contains e.g. a sinus node (sinoatrial node, SA node), an area made up of special tissue in the wall of the heart's right atrium. In the normal, healthy state this area emits periodic, recurrent electrical pulses, each of which starting a heart cycle. When the pulse from the sinus node is propagated across the walls of the atrium, it triggers contraction of the atrium for expulsion of blood into the corresponding ventricle. The pulse is carried to another tissue area in the heart which has a special delay function, the atrioventricular (AV) node, from which it is carried on special electrically conductive tissue pathways to the ventricles. It is during this phase, when the electrical pulse passes along the conductive pathways to the ventricular walls, that blood is "pumped" from the atrium to ventricle. By the time this pulse arrives to trigger contraction of the ventricles, the ventricles have been expanded by inflowing blood and are ready to contract in order to pump blood to the lungs and circulatory system. After each contraction of the ventricles, a resting period starts during which the atria fill with blood, and lasts until the SA node generates the next pulse.

Normal rhythm, i.e. sinus rhythm, arises in the SA node. A faulty rhythm or rate, i.e. arrhythmia, can develop for different reasons. For example, the pathways, made of electrically conductive tissue, to or in a ventricle may be damaged or blocked so pulses emitted in the atrium are unable to trigger any contraction of the ventricle. In such cases, an electrical stimulation pulse can be supplied by an electronic stimulation device, i.e. a pacemaker. The generating of stimulation pulses by most of the stimulation devices currently in use is synchronized with or generally dependent on the heart's intrinsic electrical activity. This activity can be monitored with sensor electrodes placed somewhere in the patient's body, e.g. in or adjacent to the heart.

These sensor electrodes in an appropriate system sense electrical voltages generated during heart activity. The electrical voltage sensed with surface electrodes on the exterior of the body has the following general morphology during a heart cycle: A low voltage pulse, the P wave, designates an atrial event, corresponding to depolarization of muscle cells in the walls of the atria, causing these walls to contract. A more complex pulse segment is referred to as the QRS complex and encompasses e.g. a large electrical pulse. This area designates a ventricular event in the form of depolarization of muscle cells in ventricular walls when these cells contract, and the heart's actual blood-pumping process is started and performed. A low voltage pulse further designates the start of repolarization of the cells in ventricular walls, i.e. recovery from their preceding contraction, and is referred to as the T wave. These pulses/pulse segments normally follow each other over time, i.e. a P wave starts first in a heart cycle, followed by the QRS complex and, finally, the T wave. These segments are not always distinguishable in the electrical voltage sensed by sensor electrodes placed in or by the heart. Thus, no T wave and often not even the QRS complex are discernible with an electrode placed in an atrium. The P wave is not visible with an electrode in the ventricle.

A typical stimulation device can operate in the following general manner: The stimulation device awaits an atrial event, signaled by corresponding electrical activity in the heart, i.e.

in practice the aforesaid P wave. If no P wave is detected within a first period of time (an atrial escape period), a stimulation pulse is sent to the atrium of the heart, stimulating muscle cells in atrial walls and causing them to contract. A ventricular event is then awaited, i.e. the device analyzes the voltage signal from the heart with respect to the presence of a QRS complex. If no such complex is detected within a second period of time (a ventricular escape interval), a stimulation pulse is sent to the ventricle, whereupon electrical activity in the atrium is again awaited. The interval between emission of stimulation pulses to the atrium and ventricle is equal to the difference in time between the first and second interval and is referred to as the AV delay. It normally corresponds to an interval lasting 100-200 milliseconds.

Normally, rate-modulating stimulation devices in current use determine the rate for emitting stimulation pulses as a function of the measurement value(s) for one or a plurality of parameters related to the physical load to which a person is subjected. These measurement values are sensed by suitable sensors devised in different ways. One such sensor can be an electrically powered flow meter, as shown in the published European patent application EP-A1 0 634 192. In other instances, the impedance of a heart ventricle is determined and, accordingly, stroke volume. Electrical impedance is measured between a stimulation electrode in a ventricle and some other electrode in the body or, especially, the heart, as is the case in U.S. patent US-A 5,417,715 which is included as a reference.

In certain embodiments, e.g. as described in the aforementioned U.S. patent, only the ongoing heart cycle is reviewed, and an appropriate time for the generating of a stimulation pulse is mainly determined from measurement values previously obtained in the same cycle, whereas measurements in previously proposed embodiments are made over a plurality of heart cycles which, in certain instances, may be well-separated in time. In principle, as is also discussed in the said U.S. patent, a well-selected or advantageous time for stimulating a heart is deemed to be when there is sufficient blood in a ventricle for it to be pumped out of same. Such a stimulation largely resembles the one which

occurs naturally in a healthy heart. So an effort should be made to select a heart rate enabling these times to be achieved or at least times which are not too far removed from them. Heart stimulator designs supplying such times are previously known through e.g. the aforementioned U.S. patent and are discussed below.

The European patent EP-B1 0 551 355 shows how the interval elapsing between two consecutive stimulation pulses is continuously varied or reset with the aid of measurement of a parameter for the heart's activity. The parameter is measured as related to a single change in the duration of the stimulated heart cycle compared to the measurement value for the preceding heart cycle. The individual changes, only made for measurement purposes, are performed with intervals between them which do not affect general pressure in the circulatory system. The parameter is impedance between e.g. an electrode placed in the heart and a pacemaker housing, and this impedance represents, or is related to, the heart's stroke volume. The ratio is formed between impedance changes, with changes of equal but opposite magnitude, in the interval between stimulation pulses, and this value is compared to a reference value which can be constant or dependent on heart rate. When hemodynamic rate optimization is proposed, the time elapsing between two stimulation pulses is reduced on individual occasions until the change in impedance stops increasing, a procedure supplying a measure of the stroke volume. Here, it must be assumed that normal stimulation is too slow and utilizes a sub-optimal stimulation rate, which should be the result with a rate corresponding to the interval used when the change in impedance stops increasing.

U.S. patent US-A 5,156,147 shows an adaptive pacemaker in which the change in the heart's pumped volume per unit of time, i.e. cardiac output (CO), is determined when heart rate increases. If the change is negative, i.e. reduced cardiac output then results, the increase in heart rate is canceled. It also notes that the increase in one possible embodiment can be also canceled if the increase in heart rate causes a drop in the increase rate for cardiac output.

SUMMARY OF THE INVENTION

The object of the invention is to set forth devices which offer simple and effective control of the emission of stimulation pulses at a rate or with a rhythm selected so the function of a heart receiving these pulses simulates, to a great degree, the function of a normally working heart, thereby preventing the imposition of needlessly heavy strain on heart muscle at any given load.

Another object of the invention is to set forth devices for delivering stimulation pulses to a person's heart at a rate or rhythm which is automatically adjusted to the work load sustained by the person.

Thus, the problem the present invention will solve is to set forth stimulation devices which determine, in a safe and effective fashion, optimal times for the generating of stimulation pulses through the use of reliable and, preferably, simple algorithms. The times for pulse emission must also be constantly adapted to a person's prevailing physical work load.

It is assumed, in the same way as in the aforesaid U.S. patent 5,417,715, that the time at which a stimulation pulse is to be generated is selected in such a way that optimal filling of a heart ventricle is achieved in each cardiac cycle. Thus, the slowest possible heart rate is thereby used for each load situation, i.e. the amount of blood required per unit of time to accommodate the physical work load, thereby imposing light strain on heart muscle. In determinations of this time and the corresponding heart rate and stimulation interval, in which the stimulation interval is the time elapsing between consecutive stimulation pulses, the stimulation interval is varied around the value selected for the moment in a way similar to the procedure described in the aforesaid patents EP-B1-0,551,355 and US-5,156,147, and a measure of the degree of filling is determined as a function of heart rate.

Heart cycle durations corresponding to a plurality of different heart rates are used, then supplying measurement values for the corresponding degree of filling.

In order to achieve simple and reliable determination of the optimal interval, an appropriate mathematical function of both heart rate and a degree of filling is selected which achieves an extreme point, e.g. a peak value, at the optimal heart rate. Such a design could also simplify and improve the efficiency of control and calculation circuits in the stimulation device. A heart rate is selected which supplies the function an extreme value, a peak value in particular, and it is subsequently used as a new optimal heart rate. One preferred mathematical function is the arithmetic product of heart rate and stroke volume raised to the second power.

According to the aforesaid U.S. patent 5,156,147, a mathematical function, cardiac output, which is the arithmetic product of heart rate and stroke volume, is used in determining the optimal heart rate. In this function the heart rate is determined at which the function displays a knee, i.e. changes from an essentially constant progression to a declining progression. A knee obtained at the intersection of two straight lines or curves is easily defined, of course, since it is found at the intersection between the lines and curves respectively. For functions obtained or measured in physical processes and which develop a knee in some area, the knee generally consists of a gentle transition between e.g. two mainly straight lines. It is then mathematically difficult to define, unequivocally, the point in the gentle transition at which the knee is located or should be located. One such determination of the location of a knee in a function in a physically determined function will then be much more difficult and unreliable than determination of e.g. a peak value for a physical function. Determination of a knee also requires more complex algorithms, which can contain different logical choices or comparisons and are, therefore, non-standard, which must be processed by the electronic calculation circuits in the stimulation device, increasing, in turn, circuit complexity. Increased circuit complexity can, in turn, increase the circuits' power consumption.

The electrical impedance measured between an electrode placed in a heart ventricle and another electrode, which can be placed inside or outside the heart, is related to the amount of blood in a heart ventricle. In particular, impedance can be determined when it reaches a peak value, which occurs when the heart ventricle contains a minimum amount of blood. Impedance can further be determined in the same heart cycle immediately before blood is ejected out of the ventricle when the nadir value for impedance is achieved, i.e. in practice immediately before the emission of a stimulation pulse, e.g. a pulse for stimulating an atrial contraction. The difference between impedance values measured in the same heart cycle constitutes a relative measure of stroke volume, so this difference, within certain limits, can be regarded as a strictly declining function of stroke volume, thereby resulting in a one-to-one ratio between the value for impedance and the value for stroke volume. Instead of a function of heart rate and stroke volume, a corresponding function of heart rate and the impedance difference can be used which has extreme values for the same values for heart rate. Thus, a function can be used which is the product of heart rate and the impedance difference raised to the second power.

When an appropriate sign is selected, the chosen function can always be made to have a peak at a given heart rate, henceforth referred to as "the optimal heart rate". The heart rate supplying this peak value can be determined in different ways.

One simple method is to have the pacemaker stimulate at a fixed rate and assign occasional intervals a length which deviates from the length of intervals in the fixed rate. Some kind of determination of stroke volume is performed, at least for the heart cycle with an altered duration, e.g. impedance is measured, and the value of the selected function can be calculated. This value for the function is compared to a corresponding value for a function calculated in the immediately preceding determination. If the new functional value proves to be larger, the interval used for determining that value is closer to the heart cycle duration corresponding to the optimal heart rate. The interval with the

altered duration is then used thereafter, and the fixed heart rate is changed to correspond to a heart cycle employing the interval's length. Otherwise, the interval used in the fixed heart rate temporarily set is closer to the heart cycle duration employing the optimal rhythm. No change in the fixed heart rate set then needs to be made.

However, it is not known in either instance whether the selected heart rate is optimal, so an individual interval is again assigned a differing duration. The duration of this interval can be selected e.g. so the change in relation to the prevailing fixed heart is in the opposite direction to the change resulting in a lower functional value in the preceding determination using a test interval with a deviating duration. In a somewhat different procedure, the difference between the duration of the new interval set and the duration of the interval corresponding to the prevailing fixed rate is assigned an arithmetic sign opposite to the sign for the immediately preceding test interval in instances in which no change was made in heart rate. In instances in which a change is made, the sign for the difference can be set at the same sign as for the difference calculated for the preceding test interval. These changes in the duration of individual heart cycles are made until two consecutive functional values have been calculated which fail to produce any change in the prevailing fixed rate. The prevailing fixed rate is then as close to the optimal value as can be determined with this stepping method.

In instances in which functional values for two consecutive test intervals are identical, it can be assumed that the optimal rate corresponds to a heart cycle duration between the durations of these test intervals. The optimal rate can then be set at a value corresponding to e.g. one heart cycle duration which is the mean value of the duration of these test intervals.

If other anomalies are present in measurement values, such as the formation of plateaus in the morphology of the selected function, this simple procedure could lead to unreliable optimization of the heart rate. In order to reduce errors caused by measurement data,

measurement values, determined for more than two intervals with different durations and weighting of the functional values calculated from these measurement values, are preferably used for determining an optimal heart rate. Thus, a measurement procedure can be used entailing variation in heart cycles, chronologically separated from each other, in which the prevailing heart rate generally employed is varied in the same way as in the aforesaid European patent EP-B1 0 551 355. The values for the selected functions are calculated for the various heart cycles set, especially for heart cycles with deviating lengths, and the heart cycle duration producing peak functional performance is determined from these functional values. The simplest way to perform a determination is to take the heart cycle duration, and associated heart rate supplying the peak value, and using this rate as the new heart rate. A more accurate and reliable determination can be made by approximating the calculated values with a simple function, e.g. a second degree function such as a parabola, and calculating the corresponding heart cycle duration from the peak value of the approximated function which is thereupon utilized in stimulating the heart.

However, this procedure can be needlessly complex and result in excessively long regulation times. Since rapid adaptation of heart rate to new and changed physiological requirements is sometimes necessary, a more appropriate procedure might be to conduct continuous searches so the duration of each stimulation interval differs from the duration of the preceding interval. Changes from the optimal heart cycle duration should then differ so little that there is no perceptible change in average blood pumping capacity while still being as large as possible to enhance accuracy in determination of stroke volume and, in particular, in determination of differences in impedance. A new optimal heart rate is calculated for each heart beat from the most recently calculated functional values. Alternately, a new optimal heart rate can be calculated after every series of a number of consecutive heart cycles with varying durations, the number being greater than two, e.g. four, calculations only being based on functional values determined for the heart cycles in this series. In one preferred embodiment, therefore, impedance measurements can be made for a plurality of consecutive heart cycles whose duration is varied from a heart

cycle duration assumed to be the best at the moment and corresponding to the optimal heart rate as above. So heart cycle duration is changed for each new cycle, and this should be performed so the average interval between stimulation pulses is essentially the same as the calculated optimal duration at the moment or equal to a reference value for duration, at least for the intervals between several consecutive stimulation pulses. The duration of intervals between stimulation pulses should also deviate in an alternating fashion from the reference value so the duration of every other interval exceeds the reference value, and the duration of every other interval is less than the reference value.

In these methods with continuous searches, the optimal heart rate, corresponding to the reference value for stimulation intervals, is constantly adjusted. Stimulation is not performed exactly so the reference value is obtained for the next heart cycle and stimulation interval but with an appropriately selected deviation so a possible new reference value can speedily and reliably be found. An additional improvement in the determination of the optimal heart rate can be achieved when calculations allow a new reference value to relate to the immediately preceding reference values, e.g. so no changes are made which are too fast and/or too large, with the aid of recursive low pass filtration of the reference values.

In the embodiments discussed above, only a few current values are compared, and no absolute reference is needed for the measured signal. So the impedance measurement only needs to be stable for a relatively brief period of time. However, impedance measurement must display good sensitivity.

DESCRIPTION OF FIGURES

The invention will now be described in detail as a non-limiting embodiment, referring to the attached drawings in which

- FIG. 1 is a diagram of a physical variable and two derived units for a heart as a function of heart rate;
- FIG. 2 is a schematic view of a heart with stimulation in only one ventricle;
- FIG. 3 is a block diagram of a stimulation device;
- FIG. 4a is an electrocardiogram;
- FIG. 4b is a diagram showing impedance, measured across a heart ventricle, as a function of time with the same time scale as in FIG. 4a;
- FIGS. 5a-5c are flow charts for procedural steps performed by a microprocessor with different determination algorithms for the set heart cycle duration and
- FIG. 6 is a flow chart for determining the value resulting in a peak for a function calculated from measurement values.
- FIG. 7 is a diagram showing the function HF as a function of the stimulation interval T.

THE PREFERRED EMBODIMENT

FIG. 1 shows different units characteristic of a heart's pumping of blood as a function of the heart's rhythm or rate. The solid line SV designates the heart's stroke volume, i.e. the amount of blood pumped by a heart ventricle in one heart cycle. When the heart rate is slow, stroke volume is directly related to the heart ventricle's maximum blood-filled volume before the ventricle contracts to eject blood. As the FIG. shows, stroke volume in the depicted area displays relatively constant progression as heart rate increases, but the curve starts a uniform, linear descent from a breakpoint. The descending curve indicates that the heart ventricle did not have enough time to fill completely with blood at fast rates. The curve CO designates the volume of blood ejected per unit of time, i.e. cardiac output, and is the product of stroke volume SV times heart rate HR. It displays corresponding progression with a breakpoint at the same value for heart rate. So this curve is generally linear up to the breakpoint, thereafter displaying an essentially constant morphology. The optimal rate at which the heart should preferably be stimulated in order to achieve the slowest possible heart rate, commensurate with accommodation of the external physical work load and supplying the lungs or circulatory system with the requisite flow of blood.

lies somewhere near the breakpoint.

The location of the breakpoint can be adaptively determined, as shown in U.S. patent 5,156,147, by increasing and reducing heart rate in steps and determining whether cardiac output increases or remains constant. However, indicating a criterion for e.g. the condition that the curve CO must be essentially constant is difficult. Another overlooked difficulty is to clearly define a breakpoint on a curve in the area in which there is a smooth transition between two curve segments with differing morphologies. So it would be desirable if an extreme point, such as a peak for a suitable function, could be sought instead. In principle, a peak can generally be determined in simple comparisons and is much easier to determine than the said breakpoint between a linear, rising or falling segment and a segment with constant progression. Various possible, new functions can be derived from the general progression of the functions shown in FIG. 1. Thus, suitable linear functions can be subtracted from the curves SV and CO. Another possibility is to form some suitable product from factors containing HR and SV in which these could be e.g. powers. One such curve HF is shown with the dashed line in FIG. 1 and was derived from the relationship $HF = HR \cdot SV^2 = HR \cdot CO$, i.e. it is a product of the curves shown with solid lines in FIG. 1.

Determination of maxima according to the above can be performed in a heart stimulator 1 (see FIG. 2 in which its connections to a heart are schematically depicted.). The stimulator or pacemaker 1 is connected by electrical leads 3 and 5 to an end electrode 7 and a ring electrode 9 connected to a heart. The stimulator 1 emits and delivers stimulation pulses to the heart across the electrodes 7, 9.

The internal structure of the stimulation device 1 is shown in the overview block diagram in FIG. 3. An impedance measurement circuit 11, connected to the electrode leads 3 and 5, is used for determining the amount of blood in the heart ventricle and, accordingly, stroke volume. At intervals determined by a microprocessor 13, it emits an e.g. 4 kHz

alternating current low-amperage signal with a brief duration. During this time, electrical impedance, i.e. electrical current in relation to the applied voltage signal, is measured. The microprocessor 13 receives the measured impedance value from the impedance measurement circuit for additional processing. Alternately, impedance can be measured between an electrode in the heart ventricle and an electrode located outside the heart, such as the metal enclosure which conventionally houses the stimulation device.

The microprocessor 13 is further connected to a read-only memory 15, ROM, and a read/write memory 17, RAM. It sends information to electronic circuits 19, for emitting stimulation pulses, containing various control circuits for e.g. detecting electrical events in the heart which designate atrial or ventricular contractions.

With the described construction, the microprocessor 13 is able to measure electrical impedance at appropriate times in order to obtain a measure of the of ventricular filling. Measuring impedance Z_1 (see FIG. 4a discussed below) can be appropriate at the time at which impedance reaches a peak value, and the heart ventricle has been emptied. This occurs at an approximately fixed time about 250 to 300 milliseconds after the stimulation pulse (cf. FIG. 4b and the discussion below). The impedance Z_2 can be further measured immediately prior to emission of a stimulation pulse. The difference $\Delta Z = Z_1 - Z_2$ between measurement values provides a measure of stroke volume. A function HF, suitable for maximization can be calculated from $HF_x = (Z_1 - Z_2)^2 \cdot HR$. And according to the above, it is approximately proportional to HF and has the same extreme values. An additional impedance measurement could also be made, in which case it is made between the described measurements at a fixed interval after the stimulation point, the interval being considerably longer than the first. A more complicated expression for a suitable function is then obtained for use in optimization.

In subsequent determination of the heart rate or corresponding stimulation interval supplying the aforesaid peak value, the time elapsing between two stimulation pulses is

varied for a plurality of consecutive heart cycles, i.e. cycle duration is varied. The impedance difference according to the above is determined for these cycles so the differences form a function of the stimulation interval or, equivalently, heart rate. As shown in the diagram in FIG. 7, the function can be determined for e.g. four different stimulation intervals, designated T_{i-1}, T_{i-2}, T_{i+1}, T_{i+}. The impedance difference for the stimulation interval T_{opt} deemed to be optimal for the moment can obviously also be easily calculated and used, even if this is unnecessary. The changed stimulation intervals can e.g. be selected to lie symmetrically in pairs around the optimal stimulation interval, such as $T_{i-1} = T_{opt} + \Delta T$, $T_{i-2} = T_{opt} - \Delta T$, $T_{i+1} = T_{opt} + 2 \cdot \Delta T$, $T_{i+} = T_{opt} - 2 \cdot \Delta T$, in which δT is a suitably small increase in the stimulation interval. As a rule, such variations in cycle durations do not cause the patient much discomfort or disrupt cardiac function, provided variation values are small. A maximum variation in cycle duration, corresponding to a rate change of ±5 heart beats a minute, is therefore permissible in many cases. δT in the example above would then correspond to a rate change of 2.5 beats a minute. Another paired, symmetrical distribution of measurement points around T_{opt} yielding a uniform distribution is provided by $T_{i-1} = T_{opt} + \Delta T$, $T_{i-2} = T_{opt} - \Delta T$, $T_{i+1} = T_{opt} - 3 \cdot \Delta T$, $T_{i+} = T_{opt} - 3 \cdot \Delta T$. In this instance, δT corresponds to a rate change of 5/3 = 1.67 heart beats/minute. The deviations in these examples are such that positive and negative deviations occur alternately, and deviation with a positive sign is followed by deviation of the same magnitude but with a minus sign, whereby each pair of deviations acquires a mean value equal to the optimal stimulation interval. The mean value of the deviations following a change in the optimal stimulation interval will also be equal to the optimal stimulation interval until the next change in the optimal stimulation interval.

An alternative to this procedure is to measure only the difference in impedance at a single change in the duration of the stimulation interval and then to use only e.g. the four or five latest difference values in determining the function's maximum HF so more "continuous" determinations are made. However, this can require a rather complex choices for the duration of the changed stimulation interval.

Alternately, e.g. in cases in which such successive changes in the duration of the heart cycle would be too uncomfortable to the patient, the procedure according to the aforesaid European patent EP-B1 0 551 335 can be used. In this procedure, the interval between two stimulation pulses during individual, non-consecutive heart cycles, separated by a plurality of heart cycles with a regular stimulation interval deemed to be optimal at the time, can be varied.

The value of the function HF according to the above can be calculated from the impedance differences and associated values for the duration of stimulation intervals. According to one simple procedure, a new, optimal stimulation interval T_{opt} yielding the largest value for the function HF can be selected from the values for which impedance measurements were made.

Alternately, a curve fitting method can be used for determining a point at which HF has a maximum value. A suitable function is selected which displays a reasonably simple progression, whose fitting to measured HF values can be expected (cf. FIG. 1), i.e. the peak of the dashed curve. One such function which can be easily calculated and used is a second degree function, i.e. a parabola. $HF_{z,par} = A \cdot (T - T_{opt,new})^2 + B$, in which A, B, $T_{opt,new}$ are constants determined during fitting, and $T_{opt,new}$ directly designates the stimulation interval value for which this function has a maximum. The second degree function can also be written $HF_{z,par} = a + bT_0 + cT_0^2$ in which a, b, c are constants. See the discussion of FIG. 6 below. If only three measurement values are used in determining the maximum, the constants can be calculated by solving a linear equation system with three unknowns. If a plurality of measurement values is to be taken into account in the determination, the constants are determined with the aid of some kind of regression analysis. For example, recursive adjustment of the constants can be made until the absolute error between the measurement values and the function falls below a predefined value.

The aforementioned determination methods are discussed in detail below in conjunction with comments on FIGS. 4a and 4b and the flow charts in FIGS. 5a-5c. FIG. 4a shows a diagram of electrical voltage at points on the body, located on opposite sides of the heart, for a heart stimulated by a pacemaker. One such voltage curve is called a surface electrocardiogram, and its general morphology was discussed above. The P and T waves appear as small positive pulses, whereas the QRS complex is characterized by a large negative pulse. The stimulation pulses are visible in the FIG. as negative, i.e. downward pointing, spikes for both atrial and ventricular stimulation, a spike appearing immediately before the P wave and immediately before the QRS complex. This means that the device according to FIG. 2 must be augmented with an atrial electrode, an associated electrical lead and control and drive circuits. Cf. U.S. patent 5.417,715 (FIG. 6) cited above. However, the stimulation pulses referred to below are only ventricular stimulation pulses. The pacemaker 1 is unable to generate a surface electrocardiogram according to FIG. 4a but can only pick up electrical voltage between points inside the body, said voltage displaying a somewhat different chronological progression. Cf. the discussion above. For example, the voltage between the end electrode 7 and the metallic surface of an enclosure housing the stimulation device 1 can be picked up and used by the stimulation device for detecting atrial and ventricular events in the known fashion. Alternately, voltage can be determined between the end electrode 7 and the ring electrode 9.

The diagram in FIG. 4b shows electrical impedance, measured e.g. between the end electrode 7 and the ring electrode 9, as a function of time for the heart for which the electrocardiogram in FIG. 4A was recorded. According to the above, the impedance is a function of the degree of heart ventricle filling and has an area comprising its largest values immediately before and/or around the T wave when the heart ventricle can be assumed to be as empty of blood as possible. The lowest values are found in the area immediately before and/or at the start of the QRS complex, corresponding to maximal filling of the heart ventricle.

The sequence of different steps performed by the microprocessor 13 will now be described, referring to the flowchart in FIG. 5a, for a first conceivable embodiment, entailing a simple search for a maximum. The method starts from starting block 501, and T_{opt} is subsequently initiated in a block 503 at an appropriately selected value T_{start}. Moreover, a variable ΔT is assigned a starting value ΔT_{start}. This variable ΔT can have both a positive and negative value and designates the time shift in the interval T_{opt} used for stimulation to be used for the next impedance measurement when the interval T_{opt} is changed for a single heart cycle to $T_{opt} + \Delta T$. A suitable time t_{start} is further determined at which the first stimulation pulse is to be Generated. In the next block 505, stimulation pulses are Generated at the times $t_{stim} = t_{start} + i \cdot T_{opt}$ in which i runs through the integers 0, 1, 2 ...., n, n being a suitably selected whole number, $n \geq 0$ in which n can advantageously have a value greater than 1.

When these stimulation pulses have been Generated, an impedance measurement is performed in the next heart cycle, and the next heart cycle's interval is set in block 507 at $T_0 = T_{opt} + \Delta T$. Impedance Z_1 is measured in block 509 after a given fixed delay D, on the order of 250-300 ms, after the last stimulation pulse. The delay D is selected so the heart ventricle in this impedance measurement is as empty of blood as possible, i.e. measurement is made when the value for impedance is about maximal. See FIG. 4b. The time at which measurement is made is then $t_1 = t_{start} + n \cdot T_{opt} + D$. An additional impedance measurement is then made in the next block 511 with the measured impedance Z_2 in the same heart cycle, immediately before the next stimulation pulse and, thus, at the time $t_2 = t_{start} + n \cdot T_{opt} + T_0 - \delta T = t_{start} + (n+1) \cdot T_{opt} + \Delta T - \delta T$. See block 511 in which δT is a small positive time. The stimulation pulse is then emitted at the time $t_{stim} = t_{start} + (n+1) \cdot T_{opt} + \Delta T$. In the block 513, a value for the function HF_z is calculated from the relationship $HF_z = (Z_1 - Z_2)^2/T_0 = \Delta Z^2/T_0$. The inverted value of the duration T_0 of an heart cycle interval corresponds to the heart rhythm. The value for HF_z is stored, with the current T_0 value, in RAM memory 17. See FIG. 3.

A determination is then made in block 515 as to whether two such values for HF_z are stored for different T_0 values. If this is not the case, the block 517 is executed, whereupon the starting value t_{start} for the next stimulation pulses emitted is set at $t_{start} = t_{start} + (n+1) \cdot T_{opt} + T_0$. The arithmetic sign for the time delay value ΔT, i.e. a positive interval shift, is set at a negative value of the same absolute magnitude and vice-versa, is then changed in a block 19, and block 505 is repeated. If block 515 found that two HF_z values were stored, block 521 is performed instead. These stored values are compared to each other in this block, and if the most recently stored value is smaller than the immediately preceding stored value, there is no need for any change in the optimal rate, and block 517 is again executed as above. Otherwise, i.e. if the latest functional value determined was larger, a change will be made, and the new starting value T_{start} is first set in block 523 to $t_{start} + n \cdot T_{opt} + 2 \cdot T_0$. Cf block 517 above. The change is made when the optimal interval T_{opt} is set at T_0 in block 525. Since the change in the duration of the heart cycle in this instance proved to yield a higher functional value, the same deviation value ΔT can be used as before in the search for an optimal heart cycle duration. After block 525, the cycle is therefore repeated, beginning with block 505.

A search for an optimal heart rate by determination of a maximum based on a plurality of values and using the general procedure described in the European patent EP-B1 0 551 355 cited above is shown in the flowchart in FIG. 5b. In principle, the procedure utilizes the same first steps 501'-513' as in the steps 501-513 described for FIG. 5a above. However, values for the parameters can differ, so ΔT can differ, and n is always ≥ 1. But the block 515' is different, and determinations are made in it as to whether four values for HF_z are stored for different T_0 values. If this is not the case, block 517', which is the same as block 517 in FIG. 5a, is executed. A new value for the time delay ΔT is then selected in block 519' in some suitable manner, e.g. as discussed above, and block 505' is executed once again. If block 515' found four HF_z values stored, block 521' is executed. This block utilizes the stored functional values for determining the value $T_{opt,new}$ for the heart cycle duration yielding a maximum value for HF_z. A simple algorithm for this will be described

below in conjunction with comments on FIG. 6. The determined value $T_{opt,new}$ will henceforth be used. To this end, the new starting value t_{start} is first set at $t_{start} + (n+1) \cdot T_{opt} + T_0 + T_{opt,new}$ in block 523'. Finally, the interval duration T_{opt} is set at $T_{opt,new}$ in block 515. Block 519' is then executed as above with a new value for time deviation ΔT, whereupon the entire process is repeated starting at block 505.

The procedural steps performed in an embodiment with more continuous adaptation of heart rate are shown in the flow chart in FIG. 5c. The procedure starts from a starting block 501", and parameter and starting values are then set in block 503". An optimal stimulation interval T_{opt} is set at an appropriate starting value T_{start}. Moreover, time deviation ΔT is assigned an appropriate positive starting value. Moreover, an appropriate time t_{start} is determined at which the first stimulation pulse is to be Generated. Moreover, values are determined for the coefficients $k_1, k_2, ..., k_m$ which are used with the fixed time deviation ΔT to form different time deviations. See below! Typical values can be m = 4 and $k_1 = 1$, $k_2 = -1$, $k_3 = 2$, $K_4 = -2$ or $k_1 = 1$, $k_2 = -1$, $k_3 = 3$, $k_4 = -3$. A stimulation pulse is Generated in the next block 505 at time $t_{stim} = t_{start}$.

A counter n in the next block 506" is assigned an initial value equal to one, and the heart cycle's next interval is then set at $T_0 = T_{opt} + K_n \cdot \Delta T$ in block 507", i.e. it is assigned a duration which differs by $k_n \cdot \Delta T$ from the optimal duration T_{opt} which is a reference value for the heart cycle and which is not directly used as a duration for an actual heart cycle. In the subsequent blocks 509"-513", the same tasks are performed as in blocks 509-513 in FIG. 5a. A query as to whether a sufficient number of new functional values are stored is then made in block 515". This is performed by comparing the counter value n with the fixed quantity m set. If this is not the case, the counter n is incremented one step in block 517", and block 507", which was described above, is executed to permit determination of additional functional values. If block 515" determines that the counter n has reached its final value, block 521" is performed. Block 521", like block 521' in FIG. 6b., compares stored functional values m to each other for determining the value T_{opt} for the heart cycle

duration yielding a maximum value for HF_z. Cf. FIG. 6. After this, a new determination of an optimal heart cycle duration is made, and the procedure switches to the above-described step 506" with initiation of the counter n, whereupon the determination loop 507"-519" is repeated m number of times.

It is obvious that the described procedures will only work with times between consecutive stimulation pulses, and no absolute times t_{min}, t_{max} need to be used. The time delays ΔT can be stated either as absolute values or expressed as a current stimulation duration T_{opt}. For example, the values ΔT = +2.5%, -2.5%, +5%, -5% of T_{opt} could be used in block 519' in FIG. 5b.

FIG. 6 shows a block diagram for a sub-routine which can be used for determining the value for heart cycle duration T_0 yielding a maximum value for HF_z. CF. blocks 521' and 521" in FIG. 5b and 5c respectively! The routine starts in block 601, whereupon the maximum and minimum values for HF_z in the four stored values are determined. They are designated $HF_{z,max}$ and $HF_{z,min}$. A determination is subsequently made in block 605 as to whether the variation in HF_z values is small, i.e. is less than a selected small value δ. If this is the case, the interval value used is acceptable, so $T_{opt,new}$ is set at T_{opt} in block 607. After this, the routine concludes in end block 609. If block 605 determined that variation exceeds the value δ, a block 611 determines whether the largest value for HF_z, i.e. $HF_{z,max}$, corresponds to the smallest value for T_0. If this is the case, the new interval $T_{opt,new}$, is set at this value in block 613. The routine then terminates again in block 609. If the determination in block 611 was negative, i.e. found that the largest value for HF_z was not obtained at the smallest T_0, block 615 is performed instead. Here, a query is made, in the corresponding manner, as to whether the largest value for HF_z is obtained at the highest T_0 value. If this is found to be the case, the new interval is set in a block at this value, i.e. $T_{opt,new}$. The routine again concludes in block 609.

If the query in block 615 resulted in a negative reply and a maximum was not obtained for

either the largest or smallest T_0 value, a maximum must be obtained for a value between these T_0 values. A more demanding calculation is then made in block 619. First, stored measurement values are approximated, as noted above, with a second degree function or parabola $HF_{a,pw} = a + bT_0 + cT_0^2$ in which a, b, c are constants which must be numerically determined, and the constant c must also satisfy the condition $c<0$ so the parabola is a type with a maximum. The T_0 value is determined which yields this maximum, and the new interval, i.e. $T_{opt,new}$ is set equal to -b/2c. The routine is then concluded in block 609. After this, new determinations are made of functional values by varying cycle duration. Thus, the method can revert e.g. to the flow chart in FIG. 5b in order to perform block 523'.

PATENT CLAIMS

1. A device for emitting electrical stimulation pulses to a heart at a variable rate (HR), comprising stimulation-emission means (19) for generating stimulation pulses, electrical control means (13, 19), connected to these means, for determining the times, which recur at the variable rate (HR) when stimulation pulses are to be generated and means (11, 13) which are connected to the control means (13, 19) and arranged to determine the heart's stroke volume (SV) at different rates, characterized in that

- calculation means (13), which are connected to the means (11, 13) for determining stroke volume and to the control means (13, 19) and which are arranged to calculate an auxiliary function (HF(HR,SV)) for two variables (HR, SV) selected in such a way that when heart rate (HR) and stroke volume as a function (SV(HR)) of heart rhythm are entered into same as the independent variables, a function is obtained for heart rate (HR) alone with an extreme point for a heart rate value corresponding to or in a range in which optimal heart function is achieved;

- means (13) which are connected to the calculation means (13), for receiving from same calculated values for the auxiliary function (HF), and to the control means (13, 19), which are arranged to determine a value for the heart rate ($HR = 1/T_{opt,new}$) at which the auxiliary function's (HF) extreme point lies and which send this value to the control means (13, 19), enabling them to control the times thereafter in such a way that they recur periodically at a frequency which essentially corresponds to this value, or enabling the average heart rate to achieve a value which essentially corresponds to this value.

2. A device according to claim 1, characterized in that the calculation means (13) is arranged to use an auxiliary function (HF(HR(SV), SV)) with an extreme point for a heart rhythm value corresponding to or lying in the range at which stroke volume (SV) at a constant load and increasing heart rate change from an essentially constant progression to a declining progression.

3. A device according to either of claims 1-2, characterized in that the calculation means (13) is arranged to calculate the auxiliary function (HF) as a product of the first variable (HR) raised to an appropriately selected power and the second variable (SV) raised to an appropriately selected power.

4. A device according to any of claims 1-3, characterized in that the calculation means (13) is arranged to calculate the auxiliary function (HF) as a product of the first variable (HR) and the second variable (SV) raised to the second power.

5. A device according to any of claims 1-4, characterized in that the means (11, 13) for determining the heart's stroke volume (SV) contain means connected to electrodes (7, 9) for measuring electrical impedance between the electrodes.

6. A device according to any of claims 1-5, characterized in that the control means (13, 19) are devised to change, on certain occasions, the interval between stimulation pulses from the interval value (T_{opt}) corresponding to the interval currently deemed to yield the optimal heart rhythm so the means (11, 13) for determining stroke volume (SV) can calculate stroke volume on these occasions.

7. A device according to any of claims 1-5, characterized in that the control means (13, 19) are devised to constantly change the interval between stimulation pulses from a reference value (T_{opt}) for the interval corresponding to the heart rate currently deemed to be optimal, these changes being made with an alternating sign, and the means (11, 13) for determining stroke volume (SV) are arranged to determine stroke volume for each heart cycle.

8. A device according to any of claims 1-5, characterized in that the control means (13, 19) is devised to constantly change the interval between stimulation pulses from a reference value (T_{opt}) for the interval corresponding to the heart rate currently deemed to

be optimal, these changes being made in such a way that the average interval between stimulation pulses is essentially equal to the reference value, and the means (11, 13) for determining stroke volume (SV) are arranged to determine stroke volume for each heart cycle.

9. A device for emitting stimulation pulses at a variable rate HR to a person's heart, comprising stimulation-emitting means (19) for emitting stimulation pulses, control means (13, 19) connected to this means for determining the times, which recur at the variable rate HR, at which stimulation pulses are to be generated and means (11) for determining impedance (Z) between an electrode (7, 9) in the ventricle of a heart and another electrode, characterized in that

- the impedance measuring means (11) are arranged to measure a change in impedance ΔZ during one heart cycle at times selected so the change in impedance ΔZ corresponds to and/or is related to the heart's stroke volume (SV) during this cycle:

- control means (13, 19) are devised to change the interval between stimulation pulses from the interval value (T_{opt}) corresponding to a reference value for heart rhythm, whereby the change in impedance ΔZ is obtained as a function of heart rate HR;

- calculation means (13), connected to the impedance-measuring means (11) for determining stroke volume and to control means (13, 19), and which are arranged to calculate an auxiliary function $HF_x(HR, \Delta Z)$, from two variables HR, ΔZ, selected so when heart rate HR and the change in impedance $\Delta Z(HR)$ as a function $\Delta Z(HR)$ of heart rate HR are inserted therein as the independent variables, a function of heart rate HR alone is obtained with an extreme point for a heart rate value corresponding to or in a range at which optimal function is achieved for the heart;

and which are arranged to send this value to control means (13, 19) for use as a new reference value for heart rate.

10. A device according to claim 9, characterized in that the calculation means (13) is arranged to determine the value heart rhythm HR value giving the function $HF_z = HR \cdot \Delta Z^2$ a maximal value and to send this value for heart rate HR to the control means (13, 19) for use as a new reference value for heart rate.

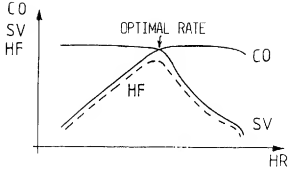

FIG.1

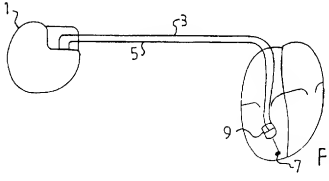

FIG.2

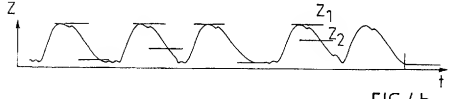

FIG.4b

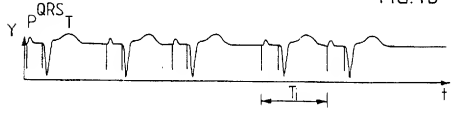

FIG.4a

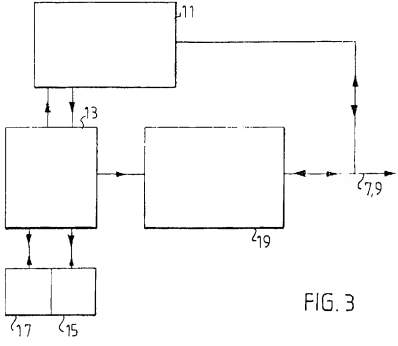

FIG. 3

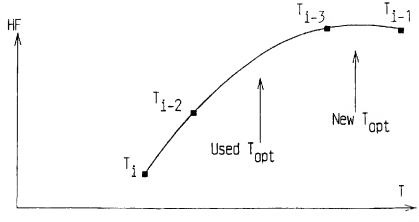

FIG.7

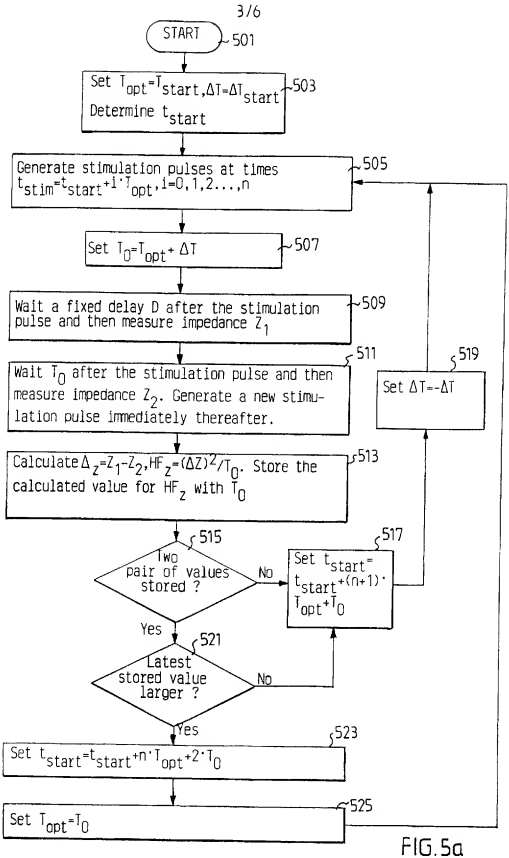
START
501
Set $T_{opt}=T_{start}, \Delta T=\Delta T_{start}$
Determine t_{start}
503
Generate stimulation pulses at times $t_{stim}=t_{start}+i \cdot T_{opt}, i=0,1,2\ldots,n$
505
Set $T_0=T_{opt}+\Delta T$
507
Wait a fixed delay D after the stimulation pulse and then measure impedance Z_1
509
Wait T_0 after the stimulation pulse and then measure impedance Z_2. Generate a new stimulation pulse immediately thereafter.
511
Calculate $\Delta_z=Z_1-Z_2, HF_z=(\Delta Z)^2/T_0$. Store the calculated value for HF_z with T_0
513
Two pair of values stored ?
515
No
Set $t_{start}=t_{start}+(n+1) \cdot T_{opt}+T_0$
517
Yes
Latest stored value larger ?
521
No
Yes
Set $t_{start}=t_{start}+n \cdot T_{opt}+2 \cdot T_0$
523
Set $T_{opt}=T_0$
525
Set $\Delta T=-\Delta T$
519

FIG.5a

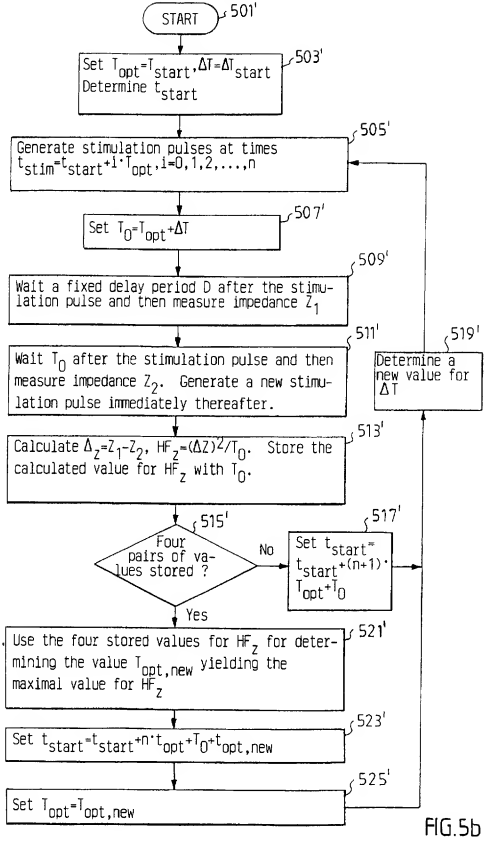
START
501'
Set $T_{opt}=T_{start}$, $\Delta T=\Delta T_{start}$ Determine t_{start}
503'
Generate stimulation pulses at times $t_{stim}=t_{start}+i\cdot T_{opt}$, i=0,1,2,...,n
505'
Set $T_0=T_{opt}+\Delta T$
507'
Wait a fixed delay period D after the stimulation pulse and then measure impedance Z_1
509'
Wait T_0 after the stimulation pulse and then measure impedance Z_2. Generate a new stimulation pulse immediately thereafter.
511'
Calculate $\Delta_z=Z_1-Z_2$, $HF_z=(\Delta Z)^2/T_0$. Store the calculated value for HF_z with T_0.
513'
Four pairs of values stored ?
515'
No
Set $t_{start}=t_{start}+(n+1)\cdot T_{opt}+T_0$
517'
Yes
Use the four stored values for HF_z for determining the value $T_{opt,new}$ yielding the maximal value for HF_z
521'
Set $t_{start}=t_{start}+n\cdot t_{opt}+T_0+t_{opt,new}$
523'
Set $T_{opt}=T_{opt,new}$
525'
Determine a new value for ΔT
519'

FIG.5b

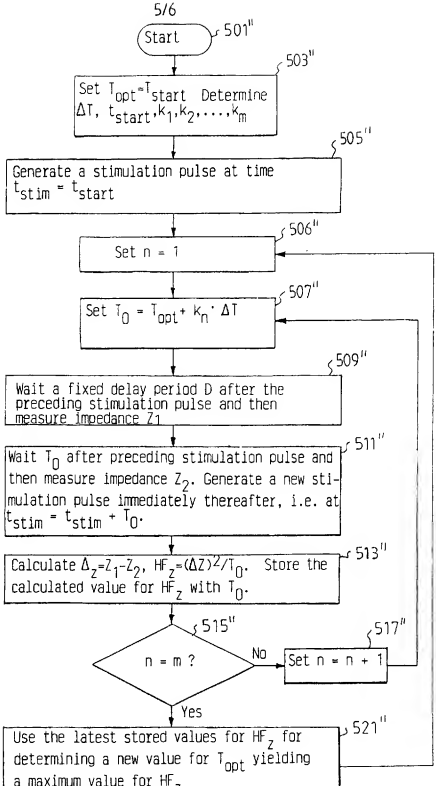
Start
501"
503"
Set $T_{opt}=T_{start}$ Determine ΔT, $t_{start}, k_1, k_2, \ldots, k_m$
505"
Generate a stimulation pulse at time $t_{stim} = t_{start}$
506"
Set n = 1
507"
Set $T_0 = T_{opt} + k_n \cdot \Delta T$
509"
Wait a fixed delay period D after the preceding stimulation pulse and then measure impedance Z_1
511"
Wait T_0 after preceding stimulation pulse and then measure impedance Z_2. Generate a new stimulation pulse immediately thereafter, i.e. at $t_{stim} = t_{stim} + T_0$.
513"
Calculate $\Delta_z=Z_1-Z_2$, $HF_z=(\Delta Z)^2/T_0$. Store the calculated value for HF_z with T_0.
515"
n = m ?
No
517"
Set n = n + 1
Yes
521"
Use the latest stored values for HF_z for determining a new value for T_{opt} yielding a maximum value for HF_z

FIG.5c

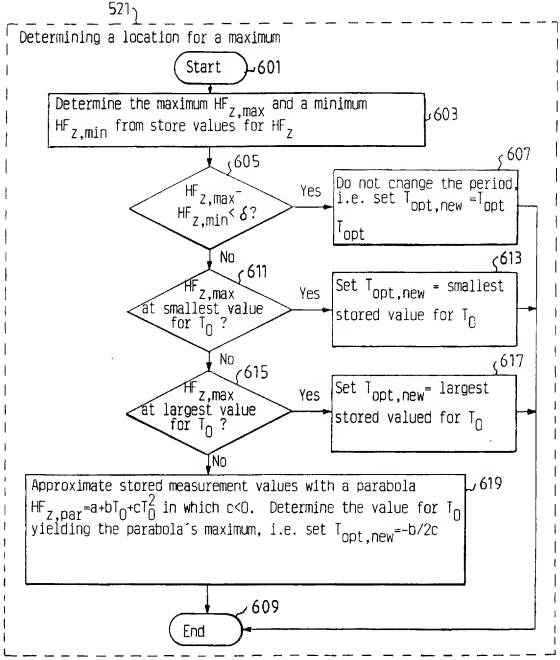
521
Determining a location for a maximum
Start
601
Determine the maximum $HF_{z,max}$ and a minimum $HF_{z,min}$ from store values for HF_z
603
605
$HF_{z,max} - HF_{z,min} < \delta$?
Yes
Do not change the period, i.e. set $T_{opt,new} = T_{opt}$
607
T_{opt}
No
611
$HF_{z,max}$ at smallest value for T_0 ?
Yes
Set $T_{opt,new}$ = smallest stored value for T_0
613
No
615
$HF_{z,max}$ at largest value for T_0 ?
Yes
Set $T_{opt,new}$ = largest stored valued for T_0
617
No
Approximate stored measurement values with a parabola $HF_{z,par}=a+bT_0+cT_0^2$ in which $c<0$. Determine the value for T_0 yielding the parabola's maximum, i.e. set $T_{opt,new}=-b/2c$
619
End
609

FIG.6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01590

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61N 1/365
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4867163 A (M.SCHALDACH), 19 Sept 1989 (19.09.89), column 21, line 35 - line 48; column 24, line 17 - line 65; column 27, line 59 - column 28, line 2	1-3,9
A	--	4-8,10
X	US 5500006 A (R.HEINZE), 19 March 1996 (19.03.96), column 4, line 7 - line 33; column 6, line 13 - line 29; column 7, line 1 - line 6	1,2,5-9
A	--	3,4,10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 January 1998	27 -01- 1998
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INTERNATIONAL SEARCH REPORT

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